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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/554,153 | 10/20/2005 | Yuelian Xu | NEU-0024 | 7731 |

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| EXAMINER | |
|---|---|
| MURRAY, JEFFREY H | |
| ART UNIT | PAPER NUMBER |
| 1624 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/554,153 | XU ET AL. | |
| | Examiner | Art Unit | |
| | JEFFREY H. MURRAY | 1624 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,5,6,9,10,15-19,21,22 and 26-28* is/are pending in the application.

4a) Of the above claim(s) *28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6,9,10,15-19,21,22,26 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/20/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. This action is in response to a restriction election filed on May 2, 2008. There are fifteen claims pending and fifteen claims under consideration. Claims 3, 4, 7, 8, 11-14, 20, 23-25, and 29-38 have been cancelled. Claim 28 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 2 2008. This is the first action on the merits. The present invention relates generally to imidazolopyrazines and triazolopyrazines that have useful pharmacological properties. The present invention further relates to pharmaceutical compositions comprising such compounds and to the use of such compounds in the treatment of central nervous system (CNS) diseases.

2. The applicants have traversed the restriction requirement and argued that there is no search burden. Examiner finds this argument unpersuasive. In order to correctly search this application, it would require more than one search to examine the bicyclic ring structure with various five-membered ring systems. For example, in the instant case, a 6-((1H-imidazol-1-yl)methyl)-2,3-dihydroimidazo[1,5-a]pyrazine core is different from a 6-((1H-imidazol-1-yl)methyl)-2,3-dihydro-[1,2,4]triazolo[1,5-a]pyrazine core. Thus, separate searches in the literature would be required. Each group's compounds are made and used independently of each other and could support separate patents. The compounds differ in chemical structures. One skilled in the art would not consider the diverse structures as functional equivalents of each other. The mere fact that there is a single similarity is not in itself a significant reason to render the whole embodiment

obvious. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants. Examiner does agree with applicants that the $R_5$ position could be searched for alkyl as well as just a propyl group. Therefore while searching Group III, $R_5$ now will be searched as a $C_1$-$C_6$ alkyl group. The restriction is deemed proper and therefore is made **FINAL**.

***Priority***

3. Acknowledgment is made of Applicant's claim for foreign priority. This application, U.S. Application No. 10/554,153, filed October 20,2005, is a national stage application of PCT/US04/13778 filed on May 3, 2004, which is a provisional application of U.S. Patent Application No. 60/468,073, filed on May 5, 2003.

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 365(c) as follows:

The oath does not claim benefit under 35 U.S.C. 365(a) of a PCT international application. Either a new oath must be submitted containing this claim or a reference must be made in the first line of the specification in regards to the claim for benefit under 35 U.S.C. 365(a).

***Specification***

4. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any of the errors of which applicant may become aware of in the specification.

***Claim Objections***

5. Claims 1, 2, 5, 6, 9, 10, 15-19, 21, 22, 26, and 27 are objected to because of the following informalities:

Claims 1, 2, 5, 6, 9, 10, 15-19, 21, 22, 26, and 27 are objected to for containing non-elected subject matter within the claims. Appropriate correction is required.

6. Applicant is advised that should claim 1 be rewritten to remove non-elected subject matter, and claim 9 be found allowable, claim 15 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

***Claim Rejections - 35 USC § 112, 1st paragraph***

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 2, 5, 6, 9, 10, 15-19, 21, 22, 26, and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds, compositions, or the pharmaceutically acceptable salts of claim 1 where $R_4$, $R_6$, $R_7$ and $R_8$ are hydrogen; $R_5$ is alkyl; and Ar is an unsubstituted or mono-substituted 2-pyridyl ring, does not reasonably provide enablement for any other compounds not previously described, or any esters, hydrates, clathrates, or prodrugs of the compounds or compositions. The specification does not enable any person skilled

in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. (*United States v. Teletronics* Inc., 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

These factors include the following:

1) *Amount of guidance provided by Applicant.* Applicant has shown guidance in how to make and synthesize the compounds and compositions of the current application wherein the R variables are those previously mentioned above. Applicant however has failed to demonstrate any compounds or compositions that fall outside the scope of the R groups mentioned previously, or any hydrates or solvates of these compounds or compositions.

The quantity of experimentation needed to make or use the invention must be considered to determine if undue experimentation is present. With regard to quantity of experimentation needed, note Wolff et. al., provided with this action, which emphasizes the many experimental factors for consideration for a successful prodrug as well as the difficulty in extrapolating data from one species to another. See p.975-7. "Extensive development must be undertaken to find the correct chemical modification for a specific

drug. Additionally, once a prodrug is formed, it is a new drug entity and therefore requires extensive and costly studies to determine safety and efficacy." Banker, et. al., Modern Pharmaceuticals, p.596. In view of all these factors undue experimentation would be required to practice the invention.

*2) Unpredictability in the art.* Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work .....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)" Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

The scope of "solvate" and "hydrate" is not adequately enabled or defined. Applicants provide no guidance as how the compounds are made more active *in vivo*. Solvates and hydrates cannot be predicted and therefore are not capable of being claimed if the applicant cannot properly enable a particular solvate.

> "Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal

> lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds. Certain molecular shapes and features favor the formation of crystals without solvent; these compounds tend to be stabilized by efficient packing of molecules in the crystal lattice, whereas other crystal forms are more stable in the presence of water and/or solvents. There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates. Vippagunta et. al. Advanced Drug Delivery Reviews 48 (2001) 3-26.

The scope of *in vivo* hydrolysable esters is not adequately enabled or defined. Applicants provide no guidance as how the compounds are made more active *in vivo*. The choice of an *in vivo* hydrolysable ester will vary from drug to drug. Therefore, more than minimal routine experimentation would be required to determine which ester will be suitable for the instant invention. The application does not provide any guidance for one skilled in the art on how the N-oxide or ester is converted to active compounds, by what mechanisms and at what site the ester will be activated, what *in vivo* enzymes are likely involved in cleaving the protected group, etc.

Applicants provide no reasonable assurance that any and all known esters will have the ability to regenerate in *vivo* to the instant compounds by one or more biological processes. It is not the norm that one can predict with any degree of accuracy a particular ester form of an active compound will be more soluble, more easily handled in formulations or more bioavailable without actual testing *in vivo*.

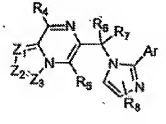
Many functional groups (eg. hydroxy,amino groups) present in drugs are capable at least in theory to being derivatized but determining what is an *in vivo* hydrolysable ester (and what is not) requires knowledge of an intended effect

(i.e. modification of an undesirable property in the parent drug- poor solubility, poor bioavailability, poor shelf-life) which is never identified by the specification.

3) *Number of working examples.* The compound core depicted with specific substituents represents a narrow subgenus for which applicant has provided sufficient guidance to make and use; however, this disclosure is not sufficient to allow extrapolation of the limited examples to enable the scope of the compounds instantly claimed or preventive agents. Applicant has provided no working examples of any compounds, compositions or pharmaceutically acceptable salts where the R and Ar variables were not those mentioned above in the present application.

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims must be provided with support in the disclosure for each member of the *Markush* group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP 608.01(p).

4) *Scope of the claims.* The scope of the claims involves all of the thousands of compounds of general formula (I):



Where $Z_1$ and $Z_2$ are N and $Z_3$ is $CR_1$, $R_5$ is alkyl and Ar is a 2-pyridyl group, thus the scope of the claims is very broad.

5) *Nature of the invention.* The nature of this invention relates generally to imidazolopyrazines and triazolopyrazines that have useful pharmacological properties. The present invention further relates to pharmaceutical compositions comprising such compounds and to the use of such compounds in the treatment of central nervous system (CNS) diseases.

6) *Level of skill in the art.* The artisan using Applicants invention would be a chemist with a Ph.D. degree, and having several years of bench experience.

MPEP §2164.01 (a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)."

***Claim Rejections - 35 USC § 112, 2nd paragraph***

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 1, 2, 5, 6, 9, 10, 15-19, 21, 22, 26, and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The scope of "aryl," "heteroaryl," "heterocycle" and "heterocyclic" requires clarification since applicants' examples in the specification are not limited to mono- or

polyfused carbocycles and heterocycles but appear to include benzo rings fused to heterocyclic rings. See definitions on p.11 and 12 of the specification. Where applicants define terms with a special meaning, they must set out the special definition with "reasonable clarity, deliberateness and precision". Note *Teleflex v. Ficosa*, 63 USPQ2d 1374; *Rexnord Corp v. Laitram Corp*. 60 USPQ2d 1851 and MPEP 2111.01.

In the absence of the specific moieties intended to effect modification by "substitution" or attachment to the chemical core claimed, the term "substituted" renders the claim in which it appears indefinite in all occurrences wherein applicant fails to articulate by chemical name, structural formula or sufficiently distinct functional language, the particular moieties applicant regards as those which will facilitate substitution, requisite to identifying the composition of matter claimed. No new matter permitted. Appropriate correction is required.

***Conclusion***

11. Claims 1, 2, 5, 6, 9, 10, 15-19, 21, 22, 26, and 27 are rejected.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey H. Murray whose telephone number is (571) 272-9023. The examiner can normally be reached on Mon-Thurs. 7:30-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a US PTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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